Non Alcoholic Fatty Liver Disease (NAFLD)

Steatosis of the liver is a usually mild and benign disease, due to several causes, as chronic viral hepatitis (mainly HCV), alcohol, drugs, diabetes, overweight, total parenteral nutrition, disorders of lipid metabolism, etc. Traditionally, steatosis of the liver is classified as alcoholic or non alcoholic. The term Non Alcoholic Fatty Liver Disease (NAFLD) represents a spectrum of conditions characterized by histologically macrovesicular hepatic steatosis in the absence of alcohol consumption. In this context, two different histological patterns exist: fatty liver alone and Non Alcoholic SteatoHepatitis (NASH).1

Portal Hypertension (PH)

To date, it is not clear whether liver steatosis per se (i.e., in the absence of severe fibrosis or liver cirrhosis) might increase portal pressure and trigger the portal hypertensive
syndrome. Further, the mechanisms by which steatosis could induce portal hypertension (PH) are not fully understood. Leptin seems to play a role in the profibrogenic responses in the liver. Activated hepatic stellate cells, the main hepatic fibrogenic cell type, express leptin as well as its receptor, Ob-RL. When treated with leptin these cells show an increased a2(I) collagen gene expression. Injected leptin leads to a greater expression of procollagen type 1, TGF-β1, and a smooth muscle actin in rats treated with CCl4 or thioacetamide. However, activated stellate cells are the most important dynamic component leading to the increase of portal pressure in patients with cirrhosis.

Relations between NASH and PH

Thus, several questions about the relationship between steatosis and portal hypertension remain to be answered:

• Does steatosis per se increase portal pressure?
• Does a “steatosis-related” portal hypertension exists (i.e., in the absence of fibrosis/cirrhosis)?
• Does portal hypertension correlate with the presence/severity of steatosis?
• Does portal hypertension differ according to the etiology of cirrhosis (viral vs alcohol vs NASH vs cryptogenic)?

PH is a severe complication of liver cirrhosis. Patients with PH are at risk to develop gastro-esophageal varices and massive gastrointestinal bleeding, ascites, hepatorenal syndrome, and hepatic encephalopathy.

Hepatic Venous Pressure Gradient (HVPG)

The portal pressure gradient is the difference between portal pressure and the pressure at the hepatic veins/inferior vena cava level; it represents the hepatic perfusion pressure. In patients with cirrhosis, portal pressure increases because of increased intrahepatic vascular resistance and increased portal blood flow. The interaction between portal blood flow and the vascular resistance that opposes that flow is defined by the Ohm’s law (ΔP = Q × R), where DP is the portal pressure gradient, Q is portal blood flow and R is the vascular resistance.

Increased resistance is due to:

1) liver architectural disturbance, with distortion of vascular architecture by fibrosis, scarring, regenerative nodules, thrombosis (mechanical or fixed component, not modifiable by pharmacological treatment), and
2) functional hepatic microcirculation alterations (active contraction of portal/septal myofibroblasts, activated stellate cells, portal venules – the so-called dynamic component, modifiable by drugs). This active intrahepatic vascular contraction is a consequence of an unbalance between vasoconstrictor substances (endothelin, angiotensin II, vasopressin, tromboxane A2, leukotrienes, etc) and vasodilators (nitric oxide-NO, CO, prostacycline, etc).

Portal blood flow in its turn increases because of enhanced production of vasodilators, increased eNOS activity and NO release, systemic and splanchnic vasodilatation, hyperkinetic circulation, hyposensitivity to vasoconstrictors.

The definition of portal hypertension is based on a pressure measurement. Portal pressure measurement may be performed directly through portal vein puncture, although it is usually determined indirectly, by subtracting the free hepatic venous pressure (FHVP) from the wedged hepatic venous pressure (WHVP). In liver cirrhosis, WHVP equals portal (sinusoidal) pressure, and FHVP equals inferior vena cava pressure. This gradient, the so-called hepatic venous pressure gradient (HVPG), accurately reflects the degree of PH in the majority of liver diseases. The technique of hepatic vein catheterization with measurement of the HVPG is safe and reproducible. The HVPG evaluation can be performed by catheterization of hepatic veins with a balloon-tipped catheter and represents the pressure in the hepatic sinusoids. In fact, the catheter in the occluded position forms a continuous column of fluid between the catheter itself and the blood in the hepatic vein, the sinusoids and the portal vein. Several studies have shown a
good correlation between direct portohepatic measurements and HVPG measurements (using a balloon catheter) both in alcoholic and viral cirrhosis. Thus, the HVPG measurement using a balloon catheter is now considered the golden standard for portal pressure evaluation.

**Clinical Picture of PH**

PH is a clinical syndrome defined by a pathological increase of the HVPG values above the normal upper limit of 5 mmHg, while clinically significant PH (CSPH) is defined by an increase in HVPG values to a threshold above approximately 10-12 mmHg. Varices do not bleed when the HVPG is below 12 mmHg.

HVPG determination is a safe and reliable tool to measure the degree of portal hypertension, with a very low rate of complications. Conscious sedation with low dose midazolam (0.02 mg/kg) increases patient comfort and willingness to undergo repeated measurements, without hepatic pressure modifications. However, it is an invasive technique, not inexpensive, which requires well-experienced hepatologists, specific equipments and expensive disposable materials.

Thus, due to these methodological and technical difficulties, the measurement of PH is not immediate and is performed only in a limited number of specialized centers. It derives that available informations on the relationship between levels of PH and clinical consequences are substantially limited, and present knowledge on PH is mainly based on the relationship between its clinical manifestations, namely gastro-esophageal varices, and clinical outcomes such as bleeding and death.

**Clinical application of HVPG measurement**

In clinical practice, HVPG measurement could have several applications, such as:

1. Evaluation of the risk of variceal hemorrhage
2. Assessment of hemodynamic response to pharmacological therapy
3. Definition of prognosis (cirrhosis and acute variceal bleeding)
4. Pre-operative evaluation of cirrhotic patients candidates to hepatic resection.

Furthermore, HVPG measurement could have a prognostic value. It has been shown that the HVPG at different cut-off levels is a predictor of long-term survival in cirrhotic patients without previous variceal bleeding at inclusion in the study. Several studies have found a significant higher survival in patients in whom HVPG levels were below the cut-off than in those with HVPG above the cut-off. The predictive HVPG value was identified between 12 and 20.8 mmHg. Further, it has been found that early measurement of HVPG in patients with acute variceal bleeding could have a negative prognostic value if ≥20 mmHg.

**NASH and Viral Hepatitis**

In patients with chronic viral hepatitis, steatosis is more frequent in hepatitis C (52%) than in hepatitis B (22%) (p = 0.03). The severity of steatosis in hepatitis C is not correlated with metabolic features, suggesting a direct role of HCV. The score of steatosis correlates with the level of HCV RNA in serum and liver, but only in patients with genotype 3. In these subjects, virological response to alfa-IFN is associated with the disappearance of the steatosis, which recurs at the time of virological relapse. Finally, steatosis grades 3-4 seem to be associated with a higher annual rate of fibrosis progression, regardless of HCV type. Further, the progression of fibrosis and of portal hypertension is influenced by the severity of steatosis and by the presence of obesity and diabetes. In particular, in patients with hepatitis C fibrosis is associated with the BMI and the severity of steatosis. Indeed, it has been shown that obese patients with HCV related CH and steatosis and diabetes show a fibrosis progression significantly higher than those with steatosis and obesity but without diabetes, and those with steatosis but without obesity.

**Clinical Picture of NAFLD and NASH**

Steatosis of the liver and NAFLD represent the most common causes of ALT elevation once other causes of liver damage have
been excluded (virus, alcohol, drugs, etc). In the majority of the patients the disease appears to be symptomless. In other subjects non-specific symptoms occur, such as fatigue, vague right upper quadrant discomfort or pain, malaise. Obesity and hepatomegaly represent the most common findings in patients with steatosis or NAFLD. Only a smaller rate of subjects show signs of chronic liver disease. In a minority of patients, the presence of ascites, variceal bleeding, anasarca indicates a decompensated liver cirrhosis.

Degree of PH in Patients with Alcoholic or non Alcoholic Etiology

To date it is not clear whether the architectural and functional alterations seen in patients with steatosis might induce a significant increase of portal pressure. In particular, when dealing with steatosis and PH, several other issues might be solved:

- Does the severity of PH differ between patients with alcohol-related and viral-related steatosis?
- Does the degree of PH correlate with the entity of steatosis?
- Does the severity of PH differ between patients with alcoholic or HCV related liver cirrhosis?
- Does the severity of PH differ by the HCV type?

Indeed, it is not yet clear whether the degree of PH differs between patients with viral and alcoholic cirrhosis, and between patients with mild vs severe steatosis. In the majority of the studies mainly subjects with alcoholic cirrhosis were included.

In a recent study, we found that the severity of portal hypertension, evaluated through HVPG measurement, does not differ by the etiology of cirrhosis (Figure 1). Further, in patients with HCV related cirrhosis, no correlation was found between HVPG and HCV genotype. Finally, the severity of steatosis (US or histological steatosis) did not correlate with the degree of the HVPG.

Other investigators found that alcoholic patients with non cirrhotic chronic liver disease and mild to severe steatosis have normal baseline HVPG, and no correlations were found between the HVPG and fibrosis, degree of steatosis and necroinflammatory activity. In these patients however, ethanol infusion significantly increased HVPG values. Thus, the authors did conclude that alcoholic patients without cirrhosis have normal portal pressure, despite liver steatosis, and that ethanol infusion increases HVPG, irrespective of steatosis, fibrosis and clinical or lab parameters. Other studies reported that HVPG did not correlate with steatosis and that alcohol ingestion markedly increased the HVPG in cirrhotic patients with already established PH.

Thus, it has been suggested that patients with NASH but without cirrhosis have no evidence of PH. Among patients with NASH, the portal hypertensive syndrome appears only in those with advanced cirrhosis. Further, although weight reduction decreases steatosis grade and fibrosis score, it is not clear whether it improves PH in patients with

![Figure 1. HVPG levels in patients with HCV-related and alcoholic cirrhosis. No significant differences in portal pressure were seen according to the etiology of cirrhosis. (From Bellis L, Castellacci R, Montagnese F, et al, ref. 10).](image-url)
Cirrhosis. Indeed, it has been shown that histological improvement might occur, with a decrease in inflammation and even in perisinusoidal fibrosis.

In contrast with these findings, other studies found a correlation between the severity of steatosis and clinical or laboratory parameters of PH, as patients with grade II/III steatosis have significantly higher frequency of hypoalbuminemia, thrombocytopenia and splenomegaly, the clinical evidence of portal hypertension.

**Cholesterol Pathway and Portal Pressure**

Recently, a relationship between cholesterol pathway and portal pressure has been suggested. Indeed, it has been found that cholesterol increases caveolin-1, a inhibitory protein of endothelial nitric oxide synthase activity (eNOS), thus decreasing eNOS activity. Further, farnesyl-PP activates RAS, a protein implicated in cell proliferation, ad thus proliferation. In its turn, geranylgeranyl-PP downregulates eNOS expression (Figure 2). Taken together, the biological actions of cholesterol and isoprenoid intermediate pathway induce a decrease of NO production, thus increasing intrahepatic resistance, which is the first phenomenon leading to portal hypertension. Simvastatin, an inhibitor of HMG-CoA reductase, counteracts these actions, increasing eNOS activity and eNOS expression and improving NO bioavailability into the liver, thus decreasing intrahepatic resistance and restoring a vasorelaxing response. For example, the brisk postprandial increase in HVPG due to volume load caused by postprandial hyperemia is markedly attenuated in patients pretreated with simvastatin but not in those receiving placebo (Figure 2).

In conclusion, given these discrepancies it is not actually clear whether steatosis in itself might affect portal pressure. However this possibility, that has been already suggested over 30 years ago, cannot be ruled out.

**References**


